AMENDMENTS TO THE DRAWINGS

Drawings

A replacement set of drawings is submitted herewith in which "1920" has been deleted from Figure 3 (Appendix A).

REMARKS

Claims 1 and 5 have been amended. New claim 8 is added. Claims 1-8 are now pending in this application. Support for new claim 8 is found in paragraph 0053 of the corresponding published application (present specification, page 13, paragraph beginning at line 20). Support for the amendments to claims 1 and 5 is found in the existing claims and the specification as discussed below. Claim 5 is amended in order to allow rejoinder upon an indication of allowability for claim 1. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Drawings and Sequence Rules

The sequence legends for Figures 2 and 3 have been amended to recite that the sequences shown correspond to SEQ ID NOS: 14 & 29, respectively.

Rejection under 35 U.S.C. § 102(b)

Claims 1-4 and 7 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Fodor, et al. (US Application No. 2001/0053519).

Fodor, et al. teach an array containing every possible 10-mer (paragraph 0122). In order to further clarify the claimed invention, claim 1 has been amended to emphasize that the capture oligonucleotides are arranged in pairs. That is, the oligonucleotide-immobilized substrate of the present invention has at least one pair of oligonucleotides which hybridize a target sequence that contains plural CpG dinucleotides. One of the pair of oligonucleotides (methylated cytosine-specific probe) has a nucleotide sequence which is complementary to or identical to the target sequence in which all C's (cytosines) other than in the CpG dinucleotides are replaced with T. The other of the pair of oligonucleotides (non-methylated cytosine-specific probe) has a nucleotide sequence which is complementary to or identical to the target sequence in which all C's including C's in the CpG dinucleotides are replaced with T. For Example:

Target sequence: acaacgaatacgaaga
methylated cytosine-specific probe: ataacgaatacgaaga or tcttcgtattcgttat
non-methylated cytosine-specific probe: ataatgaatatgaaga or tcttcatattcattat

As described in paragraph [0018] of the corresponding published application (present specification, page 4, paragraph beginning on line 9), Applicants have found that within plural

CpG islands which are located close to each other, all cytosines in such islands tend to be either methylated or non-methylated. Applicants have found that methylation of cytosines in plural CpG islands can be detected at the same time using the oligonucleotide-immobilized substrate of the presently claimed invention, which has the novel structure as claimed and as described above.

Although Fodor, et al. disclose an oligonucleotide-immobilized microarray, the immobilized oligonucleotides are random oligonucleotides, not pairs of oligonucleotides comprising a methylated cytosine-specific probe and a non-methylated cytosine-specific probe. Therefore, the presently claimed invention is not anticipated by Fodor, et al.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 102(b)

Claims 1 and 3 are rejected under 35 U.S.C. § 102(b) as being anticipated by Berlin (WO 01/38565) as evidenced by Berlin (US 6,936,419B1).

Berlin teaches a conventional array for detecting cytosine methylation. That is, while there are a set of probes directed to methylated cytosine and a set of probes directed to non-methylated cytosine, the array detects each methylation site individually (see Figure 1 of US Patent No. 6,936,419). In contrast, the presently claimed method detects "CpG dinucleotides at a plurality of sites" (claim 1). In order to further distinguish the claimed invention, claim 1 has been amended to recite that "the capture oligonucleotides correspond to a plurality of adjacent CpG islands". Support for the amendment is found in the present specification at page 9, lines 25-27. Berlin does not teach this limitation.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 102(a)

Claims 1-4 and 7 are rejected under 35 U.S.C. § 102 (a) as being anticipated by Suzuki, et al. (EP 1312685).

This ground of rejection is believed to be overcome by submission herewith of a verified translation of Applicants' priority document (Appendix B).

In view of the submission of a verified translation of Applicants' priority document, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 102(a) & (e)

Claims 1 and 3 are rejected under 35 U.S.C. § 102 (a) and (e) as being anticipated by Garner, et al. (US Publication No. 2003/0152950A1).

Garner, et al. teach a high throughput parallel analysis to determine methylation sites in DNA. In the method of Garner, et al., the potential methylation sites are numbered as shown in Figure 7. As discussed in paragraphs 0058-0062, each base is queried and "each parent probe generates at least three new probes, one for each single nucleotide polymorphism at the central base" (para. 0061). Additional query probe partners are required if multiple CpG islands are on one probe (para. 0061).

This is clearly different from the presently claimed invention. Claim 1 has been amended to recite that "the capture oligonucleotides correspond to a plurality of adjacent CpG islands". Support for the amendment is found in the present specification at page 9, lines 25-27. As pointed out above, a key feature of the presently claimed invention is based upon Applicants' discovery that CpG islands tend to be either methylated or not. By designing capture oligonucleotides that correspond to a plurality of adjacent CpG islands as recited in claim 1 as amended, sensitive and precise detection results (present specification, page 10, lines 1-6).

Applicants' claimed method is based upon detection of a plurality of CpG's while the method of Garner, et al. teaches detection of each CpG individually.

Note that this ground of rejection under 35 U.S.C. § 102 (a) is also addressed by submission of a verified translation of Applicants' priority document.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 2, 4, and 7 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Berlin (WO 01/38565) as evidenced by Berlin (US 6936419B1) in view of Fodor, et al. (US Application No. 2001/0053519).

As discussed above, Berlin teaches a conventional array for detecting cytosine methylation. That is, while there are a set of probes directed to methylated cytosine and a set of probes directed to non-methylated cytosine, the array detects each methylation site individually (see Figure 1 of US Patent No. 6,936,419). In contrast, the presently claimed method detects

"CpG dinucleotides at a plurality of sites" (claim 1). In order to further distinguish the claimed invention, claim 1 has been amended to recite that "the capture oligonucleotides correspond to a plurality of adjacent CpG islands". Support for the amendment is found in the present specification at page 9, lines 25-27. A key feature of the presently claimed invention is based upon Applicants' discovery that CpG islands tend to be either methylated or not. By designing capture oligonucleotides that correspond to a plurality of adjacent CpG islands as recited in claim 1 as amended, sensitive and precise detection results (present specification, page 10, lines 1-6).

Neither Berlin, et al nor Fodor, et al teach this limitation. Berlin et al. teach detection of each methylation site individually. Fodor, et al. merely discloses an array of 10-mers and does not teach the substrate for detecting methylation of cytosine as presently claimed. Neither reference teaches detection of a plurality of methylation sites as claimed. Accordingly, the cited references, taken separately or together, neither teach nor suggest all of the limitation of the presently claimed invention.

In view of Applicants' arguments and amendments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 2, 4, and 7 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Garner, et al. (US Publication No. 2003/0152950A1) in view of Fodor, et al. (US Application no.2001/0053519).

As discussed above, Garner, et al. teach a high throughput parallel analysis to determine methylation sites in DNA. In the method of Garner, et al., the potential methylation sites are numbered as shown in Figure 7. As discussed in paragraphs 0058-0062, each base is queried and "each parent probe generates at least three new probes, one for each single nucleotide polymorphism at the central base" (para. 0061). Additional query probe partners are required if multiple CpG islands are on one probe (para. 0061).

This is clearly different from the presently claimed invention. Claim 1 has been amended to recite that "the capture oligonucleotides correspond to a plurality of adjacent CpG islands". Support for the amendment is found in the present specification at page 9, lines 25-27. As pointed out above, a key feature of the presently claimed invention is based upon Applicants' discovery that CpG islands tend to be either methylated or not. By designing capture oligonucleotides that correspond to a plurality of adjacent CpG islands as recited in claim 1 as amended, sensitive and precise detection results (present specification, page 10, lines 1-6).

Applicants' claimed method is based upon detection of a plurality of CpG's while the method of Garner, et al. teaches detection of each CpG individually.

This deficiency is not corrected by Fodor, et al. As discussed above, Fodor, et al. merely teach an array containing every possible 10-mer (paragraph 0122). Fodor, et al. neither teach nor suggest "capture oligonucleotides [which] correspond to a plurality of adjacent CpG islands". Additionally, Fodor, et al. neither teach nor suggest pairs of capture oligonucleotides as claimed and as discussed above. Accordingly, neither Garner, et al. nor Fodor, et al. teach all of the limitations of the present claims.

In view of Applicants' amendment and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: June 20, 2006

By: Che S. Chereskin
Che Swyden Chereskin, Ph.D.
Registration No. 41,466
Agent of Record
Customer No. 20,995
(949) 721-6385

2672214
060906

aYgagcagct ctctcttcag gagtgaagga ggttaYgggc aagtYgtttt gaYgtagaYg ttttattagg
SEQ ID NO: 15
gtYgYgYgtt YgtYgttYgt tatatatYgt tYgtagtatt Ygtgtttagt ttYgtagtgg YgttYgaYgt
SEQ ID NOS: 17 and 18 SEQ ID NOS: 9 and 20 SEQ ID NOS:
YgYgttYgYg ggtagttaYg atgaggYggY gatagattag gtatagggtt ttatYgtttt tYggaggttt
21 and 22 SEQ ID NOS:23 and 24
tattattaaa taaYgttggg tttattYggg tYggaaaatt agagtttYgt Ygatttttat tttgtttttt
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ggaggagttt gagaagYgtt aagtattttt ttYgttttgY gttagattat tttagtagag gtatataagt
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SEQ ID NOS: 25 and 26
aggaagagYg gatagYgatt tttaaYgYgt aagYgtatat tttttaggt agYgggtagt agtYgtttta
SEQ ID NOS: 27 and 28
gggagggaYg aagagattta gtaatttata gagttgagaa atttgattgg tatttaagtt gtttaattaa

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SEQ ID NO: 16
tttagcggtt agttaatgtt attaaagaga tgattgagaa ttggtacgga gggagtcgag 19~~20~~

Fig. 3